MINUTES

MEETING WITH PHARMANEX

APRIL 7, 1997 0222 '98 JAN -8 A9:28

Attendees:

Pharmanex:

Michael N. Chang, Chief Scientific Officer and Sr V.P. Research & Development
Janice Thompson, Vice President for Scientific Affairs
Eugene Lamber, Covington & Burling
David Heber, M.D., Ph.D., Professor and Director UCLA Center for Human Nutrition
Koji Nakanishi, Columbia University, Professor of Organic and Natural Products Chemistry
William McGlashan, President
Henry S. Burdick, Chairman & CEO
Kim Anderson, Covington & Burling
Jan Burdick, Director of Human Resources

FDA:

Bradford Williams, Director, Division of Labeling and Nontraditional Drug Compliance
Philip Derfler; Office of General Counsel
William Russell, Consumer Safety Officer, Nontraditional Drug Compliance
A. Joel Aronson, Team Leader, Nontraditional Drug Compliance
David Orloff, M.D., Medical Officer
Solomon Sobel, M.D., Director, Division of Metabolism and Endocrine Drug Products
Ilisa Bernstein, Senior Science Policy Adviser
David M. Fox, Associate General Counsel
William Berlin, Chemistry Reviewer
Stephen Moore, Chemistry Team Leader
Jackie Leung, Deputy Director. Division of Labeling and Nontraditional Drug Compliance
Ron Steigerwalt, Pharmacology Team Leader
John Loh, Acting Team Leader, Prescription Drug Compliance
Gloria Troendle, M.D., Deputy Director, Division of Metabolism and Endocrine Drug Products
Ann Witt, Counselor to the Deputy Commissioner for Policy
Beth Yetley, Director, Office of Special Nutritionals
Patti Gupta, Inspector, Phoenix Resident Post*
Jack Nicholson, Inspector, Phoenix Resident Post*
Ron Koller, Inspector, Canoga Park, CA*
Tom Savage, Seattle District Office*
Greg Mercer, Seattle District Office*
* attendance via teleconference

97P-0441

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Background:

In November, 1996, Pharmanex began marketing a product called "Cholestin" with claims for lowering blood cholesterol. On March 18, 1997, we received a complaint from a pharmacist who was concerned about the product containing a HMG CoA reductase inhibitor "e.g., lovastatin". An assignment was faxed to the Phoneix Resident Post on March 21, 1997. Following the FDA inspection of the firm by Ron Koller on March 24, 1997, the firm requested a meeting on April 2, 1997, through their lawyer, Eugene Lambert, to discuss the product. The firm agreed to cease distribution until after the meeting.

Notes:

- Gene Lambert opened the meeting by stating the purpose of the meeting was to describe the product, its origin, and its uses.

- Michael Chang presented the scientific background. Notably:
  - the *Monoscus* genus has 4 species from which 128 strains have been isolated
  - more than 20 strains contain HMG CoA reductase inhibitors
  - traditional uses of *Monoscus purpureus* Went are as a food & spice, preservative & coloring agent, wine making, traditional Chinese medicine as a heart tonic, GI problems, improving circulation, and as an antifungal
  - the Cholestin manufacture process includes pure yeast rice made by traditional solid fermentation process
  - "No other bacterial or fungal growth is allowed to contaminate the process that may produce HMG CoA reductase inhibitors"
  - "Nothing, including pharmacologically active substances, is added to Cholestin"
  - "Cholestin is not concentrated by any method (e.g., extraction)"
  - a strain is selected to produce the best HMG CoA reductase inhibitor concentration

- the question was asked about how the nutritional benefits of the product occur. The answer was the product entered the food chain as phytochemicals. The firm feels this product is not a traditional nutrient nor is there a limit on what can be a dietary supplement.

- the FDA's position is that the product is a drug under 201(g)(1)(B) based on the totality of the product labeling, ingredients, and trade name. The firm feels the claims are excluded from the drug definition and represent structure/function claims under DSHEA. The item was sold as food before any chemical entity was studied. This is a dietary supplement with pharmacological action. Gene Lambert expressed the opinion that 403(r)(6) has been complied with by providing its structure/function claims to the FDA and including the disclaimer on its label.

- The firm raised the issue that oat bran has been approved under NLEA for lowering cholesterol and the firm equated this as accepting this claim for structure/function status under DSHEA. Phil Derfler explained that the oat bran document under NLEA pertains to

disease rather than structure/function authority.

- Dr Chang stated that the uniformity in their process is achieved by using the levels of HMG CoA reductase inhibitor as a marker. He states they have isolated eight (8) structures so far that have HMG CoA reductase inhibitor activity. Approximately half of the HMG CoA reductase inhibitor concentration is Mevinolin (which is the previously used name for Lovastatin)

- Dr Sobel questioned the firm on whether it's common practice for a food product to use a drug product as a marker. He further asked if this is a conventional way of processing a nutritional supplement. The question was side-stepped by Dr. Chang saying that markers give an indication of the process and that their product was standardized to contain 0.4% HMG CoA reductase inhibitor per capsule. Again, Dr Sobel asked whether this is a precedent for standardizing a food supplement based on a drug compound. Dr Chang again avoided answering the question by stating that any batches that failed to meet the 0.4% standard were rejected. The firm contends that the 0.4% standardization is strictly for product uniformity.

- The FDA considers elevated cholesterol to be a disease. NDAs for cholesterol-lowering agents must demonstrate cholesterol lowering as the endpoint rather than morbidity and mortality. Lowered cholesterol has been associated with the benefit of prevention. Epidemiologic data demonstrated that total cholesterol of 180 and up enhances the danger of coronary artery disease. Therefore, hypercholesterolemia is classified as a disease and, therefore, Cholestin is considered to be a drug and an unapproved new drug.

- The firm claims that seventeen (17) studies have been done in China. A new one in the US is currently underway looking for the efficacy in triglyceride lowering.

- Gene Lambert denied their product contains Lovastatin as did Dr Chang who disputed Seattle's analysis, saying that his analysis showed the capsules to contain 1.18mg of "Mevinolin which tests like Lovastatin." It was pointed out the "Mevinolin" is the previous name for Lovastatin. Dr Chang made no reply.

- The firm left the conference room to allow the FDA to meet among themselves.

Summary to the firm:

- The firm was given the FDA's conclusion that Cholestin is a drug based on its labeling and formulation with added emphasis given to the fact that the product's trade name is a drug claim as well. The product cannot be marketed as it stands. The firm was thanked for its willingness to suspend distribution of the product and we hoped they would agree to continue the suspension.

- Gene Lambert stated they were not prepared to continue withholding marketing of the product and assumed the objections could be overcome by labeling changes.

- He was reminded that the problem involves labeling, the product name, and the contents of the product. We were not prepared to enter into a speculative review of the corrective measures but said he should get together with his clients to work out a solution.

- Gene Lambert said he would give an answer this afternoon regarding their position.

Prepared by: _____ _____
William Russell Date
Consumer Safety Officer, Nontraditional Drug Compliance Team

Concurrence: _____ _____
Bradford Williams Date
Director, Division of Labeling and Nonprescription Drug Compliance

_____ _____
A. Joel Aronson Date
Team Leader, Nontraditional Drug Compliance Team

_____ _____
Phil Derfler Date
Office of General Counsel

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